DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

**NDA APPROVAL**

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manger, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) dated and received October 28, 2015, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EPCLUSA® (sofosbuvir and velpatasvir) tablet, 400 mg/100 mg.

This new drug application provides for the use of EPCLUSA® (sofosbuvir and velpatasvir) tablet for the treatment of adult patients with chronic hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, or 6 infection:

- without cirrhosis or with compensated cirrhosis; and
- with decompensated cirrhosis for use in combination with ribavirin.

We also acknowledge receipt of the information related to the EPCLUSA® (sofosbuvir and velpatasvir) tablet, 400 mg/100 mg, for the Gilead Access Program that was reviewed as a part of this application.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

## IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container labels submitted on May 18, 2016 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Container Labels for approved NDA 208341**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Linda C. Onaga, MPH
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6360
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code* **20903** *if shipping via United States Postal Service (USPS).*
*Use zip code* **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

## ADVISORY COMMITTEE

Your application for EPCLUSA was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and outside expertise was not necessary as there were not significant issues that would benefit from an advisory committee discussion.

## REQUIRED PEDATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to less than 3 years because necessary studies are impossible or highly impracticable. This is because spontaneous HCV clearance is possible and very few patients in this age group require treatment.

We are deferring submission of your pediatric studies for ages 3 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3092-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus infection.

| | |
|---|---|
| Final Protocol Submission: | 06/2016 |
| Study Completion: | 03/2019 |
| Final Report Submission: | 09/2019 |

3092-2 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C virus infection.

| | |
|---|---|
| Final Protocol Submission: | 06/2016 |
| Study Completion: | 10/2020 |
| Final Report Submission: | 04/2021 |

Submit the protocols to your IND 118605, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- assess a signal of a serious risk of increased toxicity, including rhabdomyolysis, as a result of a potential pharmacokinetic-based interaction between atorvastatin and the components of EPCLUSA (sofosbuvir and velpatasvir);
- identify unexpected serious risks in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) concurrently with HIV antiretroviral therapy,
- assess a known serious risk of toxicity due to elevated exposure to tenofovir levels in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) with a tenofovir-containing regimen;
- assess a known serious risk of virologic failure and persistence of treatment-emergent drug resistant viral populations in hepatitis C virus genotype 3 patients with cirrhosis that may limit future re-treatment options;
- identify serious adverse events including progression of liver disease, liver-related mortality, or liver failure requiring liver transplantation in patients with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with EPCLUSA (sofosbuvir and velpatasvir).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to:

- assess a signal of a serious risk of increased toxicity, including rhabdomyolysis, as a result of a potential pharmacokinetic-based interaction between atorvastatin and the components of EPCLUSA (sofosbuvir and velpatasvir);
- identify unexpected serious risks in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) concurrently with HIV antiretroviral therapy,
- assess a known serious risk of toxicity due to elevated exposure to tenofovir levels in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) with a tenofovir-containing regimen;
- assess a known serious risk of virologic failure and persistence of treatment-emergent drug resistant viral populations in hepatitis C virus genotype 3 patients with cirrhosis that may limit future re-treatment options;
- identify serious adverse events including progression of liver disease, liver-related mortality, or liver failure requiring liver transplantation in patients with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with EPCLUSA (sofosbuvir and velpatasvir).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3092-3 Conduct a drug interaction trial to evaluate the interaction between sofosbuvir and velpatasvir and atorvastatin.

The timetable you submitted on June 7, 2016, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 08/2016 |
| Trial Completion: | 12/2016 |
| Final Report Submission: | 05/2017 |

3092-4 Submit the final clinical report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5), titled "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human immunodeficiency Virus (HIV)-1 Coinfection," to provide safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 08/2016 |
| Final Report Submission: | 12/2016 |

3092-5 Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with sofosbuvir and velpatasvir to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 06/2017 |
| Final Report Submission: | 06/2018 |

3092-6 Collect, analyze, and submit data from the HCV infected subjects with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 08/2016 |
| Trial Completion: | 05/2018 |
| Final Report Submission: | 05/2019 |

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.